REMARKS/ARGUMENTS

Claims 1-17 were pending in the above-captioned application. Claims 8, 9 and 13-17 have earlier been withdrawn from consideration. Claim 1 has now been amended to more particularly point out and distinctly claim that which Applicants consider to be their invention. As a result of amending and restricting claim 1, claims 2, 4 and 10 have been cancelled. Two new claims, claims 18 and 19, have been added. Basis for these claims is found on page 6 of the specification.

Upon entry of the above-made amendments, therefore, claims 1, 3, 5-9, 11-19 will be pending in the current application. The amended claims are fully supported in the specification as originally filed. The amendments to the Claims do not add new matter. Applicants respectively request that the amendments be entered.

The following remarks, in conjunction with the above amendments, are believed to be fully responsive to the Office Action.

THE REJECTION UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Vaughn U.S. Patent 5,242,392 ("Vaughn"). In response, Applicants submit that the rejection should be withdrawn for the reasons stated below.

As noted above, claim 1 has been amended to recite that the invention is directed to administration of a gas-containing contrast agent by continuous infusion, wherein the contrast agent is delivered from the upper extremity of an essentially vertically positioned syringe.

A finding of anticipation under 35 U.S.C. 102 requires the disclosure in a single prior art reference of each element of the claim under consideration. *W.L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Found. v. Genetech Inc.*, 927 F.2d 1565, 18 USPQ 2d 1001, 1010 (Fed. Cir. 1991).

The present invention is drawn to administration of a gas-containing contrast agent by continuous infusion. The contrast agent is delivered from an upper extremity of an essentially vertically positioned delivery vessel, and is admixed with a flushing medium prior to administration to a subject. The present invention has identified a solution to the problem of administering a gas-containing contrast agent by infusion. A problem with the continuous infusion of gas-containing diagnostic contrast agents arises from the tendency of gas-containing components to float, since this will lead to inhomogenities forming within vessels such as power-driven syringes which may be used to administer the contrast agent. This may, for example, lead to an increase in microbubble concentration in the upper part of such a vessel and/or to changes in size distribution occurring at various points within the vessel as larger microbubbles float more rapidly than smaller microbubbles. By combining delivering from the top of a vertically positioned syringe and admixing with a flush medium prior to administration to a patient, the segregation is minimized and enhanced product homogeneity is achieved. By using a syringe as the delivery reservoir and placing this in a vertical position, with the outlet pointing upwards, the effects of floatation separation is greatly reduced, as further explained in the specification on page 3 and 4. The admixing with a flushing medium further enhances the homogeneity of the contrast agent that is delivered to the patient, e.g. by reducing the residence time of the agent in connecting tubes etc. It is further preferred that the syringe is positioned so that the bulk flow direction of the gas-containing contrast agent during expulsion is the same as the direction of segregation of the dispersed gas-bubble phase, i.e. upwards, since this will assist in counteracting the formation of concentration gradients of the dispersed gas-bubbles during administration. Thus, for example, in the case of dispersions such as gas-containing contrast agents in which the

dispersed phase is susceptible to flotation, it is preferred to use delivery vessels positioned for upward delivery.

Vaughn discloses an intravenous piggyback flush apparatus for administration of medicaments into a patient by force of gravity. The Applicants still finds that Vaughn does not describe administration by infusion wherein a segregating dispersion is admixed with a flushing medium prior to administration to the patient as outlined in our response dated March 23., 2004. In addition, the instant claims have been restricted to administration of gas-containing contrast agents from an essentially vertically positioned syringe. As the medicaments in Vaughn are delivered from drip-bags, with the outlet pointing downwards, Vaughn does not teach each element of the claim under consideration, i.e. the amended claim 1.

Thus, Applicants respectfully submit that the Examiner's rejection under 35 U.S.C. 102 (b) has been overcome and/or obviated and respectfully request that the rejections be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being obvious over Vaughn in view of Remington, The Science and Practice of Pharmacy 19th edition, pages 1552-1554 ("Remington"). Further, claims 1-7, 10-12 are rejected under 35 U.S.C. 103(a) as being obvious over Vaughn in view of Remington and further in view of Unger, WO 97/48337 ("Unger"). In response, Applicants submit that each of these rejections should be withdrawn for the reasons stated below.

The Applicant finds that the combined teaching of Vaughn and Remington does not render the instant amended claims obvious for the reasons stated below.

Vaughn discloses an intravenous piggyback flush apparatus for administration of medicaments into a patient by force of gravity. As outlined in our previous response Vaughn does not teach administration wherein a gravity segregating dispersion is admixed with a flushing medium. Conventional drip bags, being emptied from the bottom of the bag, are

described by Vaughn. Further, Vaughn does not describe administration of gas-containing contrast agents.

Remington describes various ways of administering a medicament. These are (page 1552, second paragraph): Direct intravenous injection, Volume control method and Piggyback method. The piggyback method is the only method described that has flushing medium in a separate container. For this method it is described that the medicament is entered "on top" of a primary IV fluid to e.g. reduce irritation (page 1553, second paragraph). Remington describes a method switching between administration of a drug solution and a intravenous fluid, and to achieve this, one container is hung lower than the other container. Further, Remington does not describe administration of a gas-containing contrast agent delivered from an upper extremity of a vertically positioned syringe, or admixture with a flushing medium.

A combination of Vaughn and Remington does not teach admixing of a gas-containing contrast agent delivered from a essentially vertically positioned syringe with a flushing medium prior to administration. Hence, Applicants submit that the rejection based on the combination of Vaughn and Remington should be withdrawn.

Unger is drawn to ultrasound contrast agents and delivery of such to a patient. However, as outlined in our previous response also Unger fails to teach admixing of the contrast agent with a flushing agent. He also fails to teach administration by continuous infusion, i.e. non-interrupted administration of the contrast agent and simultaneous admixture with flushing medium over time. Unger describes that diagnostic artifacts such as shadowing may be reduced by controlling the rate of administration of the contrast agent and/or by

administering a flush such as normal saline after administration of the contrast agent. Contrast agent administration rates of 1-8 x 10^6 vesicles/kg-sec or 1 x 10^{-7} to 3 x 10^{-3} cc gas/kg-sec and flush rates of 0.01-2.4 ml/sec are suggested; the contrast agent is typically administered over a period of 5-20 seconds, and any subsequent flush is typically administered over a period in the range 10 seconds to 10 minutes. The suggested flush rates of 0.01-2.4 ml/sec (claim 88), i.e. 0.6-144 ml pr. min. illustrate that Unger is restricted to bolus injection. Administration of the flushing medium with a higher rate than a few ml/minute over several minutes could generally lead to pain for the patient. As given in our specification an appropriate flow rate for the flushing medium during continuous infusion is 0.5-2 ml/min, or up to 5 ml/min. (page 6, 4th paragraph), for infusion periods of up to an hour. One aspect of the Unger document is to deliver the contrast agent to the patient in a way that reduces the diagnostic artifacts in the diagnostic images (page 65). Unger suggests that the rate of administration of the contrast agent relate to the occurrence of diagnostic artifacts, and he suggests an administration time for the contrast agent of 5 seconds (page 66, first paragraph). To promote the transport of the contrast agent from the injection site into the bloodstream, a flush may be administered to push or wash the contrast agent into the bloodstream (page 70). With regard to avoiding artifacts in the image his solution lies in speed of the flushing medium. Further, as the contrast agent is injected so quickly, and hence as the contrast agent reservoir is in the delivery vessel for such a short time, the shape and position of Unger's contrast agent delivery vessel is not essential. The problem associated with continuous infusion of gas-containing contrast agents arising from the tendency of gas-containing components to float, leading to inhomogenities in delivery vessels is not a topic in Unger, as it is not directed to infusion. Infusion in normally defined as the continuous intravenous administration of an agent over a sufficiently long time period to obtain a steady-state level of the agent in blood.

Hence, there is no indication by Unger that the syringe should be positioned vertically with the outlet pointing upwards. As Vaughn and Remington, Unger fails to teach administration by continuous infusion from the upper extremity of a vertically positioned syringe and thereafter admixing with a flushing medium. So, combining the method and

apparatus of Vaughn, or Remington, and administering the contrast agents of Unger would not lead to the invention instantly claimed.

As argued above, claim 1 and subsequent claims, are not obvious based on the references, as none of these, alone or combined, suggest continuous infusion by admixing a gas-containing contrast agent delivered from the upper extremity of a vertically positioned syringe with a flushing media prior to administration to enhance product homogeneity.

Thus, Applicants respectfully request that the rejections be withdrawn.

CONCLUSIONS

In view of the amendments and remarks herein, Applicants believe that each ground for rejection or objection made in the instant application has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the current application are respectfully requested.

The Examiner is invited to telephone the undersigned in order to resolve any issues that might arise and to promote the efficient examination of the current application.

Respectfully submitted,

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